"SEQUENCE LISTING" and the text file is identical to the information originally submitted with the specification. Accordingly, no new matter has been added to the Application.

Conclusion

Early and favorable action is earnestly solicited.

Respectfully submitted,

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February 10, 2003
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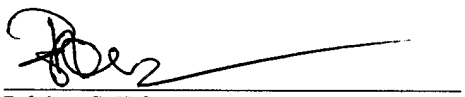
I hereby certify that this correspondence is being deposited with the U.S. Postal Service First Class Mail in an envelope addressed to the Assistant Commissioner for Patents, Washington, D.C. 20231 February 10, 2003.



Palaiyur S. Kalyanaraman
Registered Representative

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File No. IN01157K-US

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of: Saksena, *et al.*

Serial No.: 09/909,062

Group Art Unit: 1648

Filed: July 19, 2001

Examiner: D. Wortman

For: NOVEL PEPTIDES AS NS3-SERINE PROTEASE INHIBITORS OF HEPATITIS C VIRUS

Marked-Up Preliminary Amendment under 37 C.F.R. §1.121

Honorable Commissioner of
Patents and Trademarks
Washington, D.C. 20231

Sir:

The following Marked-Up Amendment shows all changes made to the specification in the enclosed Preliminary Amendment.

In the specification:

(1) Please replace the title of Example 1, at the top of page 101, with:

- -**Example I: Solid Phase Synthesis of Ac-EEVVP-nV(CO)-G-OH** (SEQ ID NO: 1)- -

(2) Please replace the last full paragraph of page 106 with:

- - **Step III.** Synthesis of Fmoc-Val-Pro-nVal(dpsc)-Gly-PAM resin (SEQ ID NO: 2)

The compound of step II above (100 mg) was transferred to a fritted polypropylene tube and was deprotected according to Procedure C. A ninhydrin assay on a small aliquot gave dark blue resin and solution, indicating a high yield

for the deprotection. The resin was resuspended in DMF (1 mL) and coupled to Fmoc-Val-OH (51 mg, 0.15 mmol) according to Procedure A. A small aliquot was taken for qualitative ninhydrin analysis which showed colorless beads and a dark red solution indicating a high yield of coupling. - -

(3) Please replace page 107 with:

- -107

Step IV. Synthesis of Fmoc-Val-Val-Pro-nVal(dpsc)-Gly-PAM resin (SEQ ID NO: 3)

The compound of the previous step (100 mg) was deprotected according to Procedure C. A ninhydrin assay on a small aliquot gave dark blue resin and solution showing a high yield for the deprotection. The resin was resuspended in DMF (1 mL) and was coupled to Fmoc-Val-OH (51 mg, 0.15 mmol), according to Procedure A for 20 hours. A small aliquot was taken for qualitative ninhydrin analysis which showed colorless beads and solution indicating a high yield of coupling.

Step V. Synthesis of Fmoc-Glu(OtBu)-Val-Val-Pro-nVal(dpsc)-Gly-PAM resin (SEQ ID NO: 4)

The compound of the previous step (100 mg) was deprotected according to Procedure C. A ninhydrin assay on a small aliquot gave dark blue resin and solution showing a high yield for the deprotection. The resin was resuspended in DMF (1 mL) and was coupled to Fmoc-Glu(OtBu)-OH (64 mg, 0.15 mmol), according to Procedure A for 5 hours. A small aliquot was taken for qualitative ninhydrin analysis which showed colorless beads and solution indicating a high yield of coupling.

Step VI. Synthesis of Fmoc-Glu(OtBu)-Glu(OtBu)-Val-Val-Pro-nVal(dpsc)-Gly-PAM resin (SEQ ID NO: 5)

The compound of the previous step (100 mg) was deprotected according to Procedure C. A ninhydrin assay on a small aliquot gave dark blue resin and solution showing a high yield for the deprotection. The resin was resuspended in DMF (1 ml) and was coupled to Fmoc-Glu(OtBu)-OH (64 mg, 0.15 mmol),

according to Procedure A for 5 hours. A small aliquot was taken for qualitative ninhydrin analysis which showed colorless beads and solution indicating a high yield of coupling.

Step VII. Synthesis of Ac-Glu(OtBu)-Glu(OtBu)-Val-Val-Pro-nVal(dpsc)-Gly-PAM resin (SEQ ID NO: 6)

The compound of the previous step (100 mg) was deprotected according to Procedure C and acylated according to Procedure E. The resin was vacuum dried and a small aliquot was taken for qualitative ninhydrin analysis which showed colorless beads and solution indicating a high yield of coupling.

- -

(4) Please replace page 108 with:

Step VIII. Synthesis of Ac-Glu(OtBu)-Glu(OtBu)-Val-Val-Pro-nVal-(CO)-Gly-PAM resin (SEQ ID NO: 7)

The compound of the previous step (100 mg) was subjected to semicarbazone hydrolysis Procedure F.

Step IX. Synthesis of Ac-Glu-Glu-Val-Val-Pro-nVal-(CO)-Gly-OH (SEQ ID NO: 8)

The resin of the previous step (100 mg) was subjected to HF cleavage condition (Procedure G) to yield the desired crude product. The material was purified by HPLC using a 2.2 X 25 cm reverse phase column, containing a C-18 resin comprised of 10 micron size gel particles with a 300 angstrom pore size, eluting with a gradient using 5-25% acetonitrile in water. Analytical HPLC using a 4.6 X 250 mm reverse phase column, containing a C-18 resin comprised of 5 micron size gel particles with a 300 angstrom pore size, eluting with 5-25% acetonitrile (containing 0.1% trifluoroacetic acid) showed one peak at 17.5 minutes. Low resolution mass spectrum confirmed the desired mass (MH^+ 798.5).

Table of Compounds synthesized according to Example I

COMPOUND NAME	SYNTHESIS
Ac-EEVVP-nV-(CO)-G-OH (SEQ ID NO: 9)	example I
Ac-EEVV-Sar-nV-(CO)-G-OH (SEQ ID NO: 10)	step II: used Fmoc-Sar-OH
Ac-EEVV-Aze-nV-(CO)-G-OH (SEQ ID NO: 11)	step II: used Fmoc-azetidine-OH
Ac-EEV-G(Chx)-P-nV-(CO)-G-OH (SEQ ID NO: 12)	step III: used Fmoc-Gly(CHx)-OH
Ac-EEVFP-nV-(CO)-G-OH (SEQ ID NO: 13)	step III: used Fmoc-Phe-OH
Ac-EEVIP-nV-(CO)-G-OH (SEQ ID NO: 14)	step III: used Fmoc-Ile-OH
Ac-EEVV-dlPip-nV-(CO)-G-OH (SEQ ID NO: 15)	step II: used Boc-d,l-pipecolic acid
Ac-EEVV-Tiq-nV-(CO)-G-OH (SEQ ID NO: 16)	step II: used Fmoc-Tiq-OH
Ac-EEVV-C(Me)-nV-(CO)-G-OH (SEQ ID NO: 17)	step II: used Fmoc-Cys(Me)-OH
Ac-EEVV-C(O2,Me)-nV-(CO)-G-OH (SEQ ID NO: 18)	step II: used Fmoc-Cys(O2,Me)-OH
Ac-EEVV-C(2-AcOH)-nV-(CO)-G-OH (SEQ ID NO: 19)	step II: used Fmoc-Cys(2-AcOtBu)-OH
Ac-EEVV-M(O2)-nV-(CO)-G-OH (SEQ ID NO: 20)	step II: used Fmoc-Met(O2)-OH
Ac-EEVV-P(4t-Bn)-nV-(CO)-G-OH (SEQ ID NO: 21)	step II: used Boc-Pro(4t-Bn)-OH

- -

(5) Please replace page 109 with:

Ac-EEVV-P(4t-Bn(4-OMe))-nV-(CO)-G-OH (SEQ ID NO: 22)	step II: used Boc-Pro(4t-Bn(4-OMe))-OH
Ac-EEVV-P(4t-allyl)-nV-(CO)-G-OH (SEQ ID NO: 23)	step II: used Boc-Pro(4t-allyl)-OH
Ac-EEVVD-nV-(CO)-G-OH (SEQ ID NO: 24)	step II: used Fmoc-Asp(OtBu)-OH
Ac-EEVVE-nV-(CO)-G-OH (SEQ ID NO: 25)	step II: used Boc-Glu(OtBu)-OH
Ac-EEVVF-nV-(CO)-G-OH (SEQ ID NO: 26)	step II: used Fmoc-Phe-OH
Ac-EEVV-P(4t-AcOH)-nV-(CO)-G-OH (SEQ ID NO: 27)	step II: used Boc-Pro(4t-AcOBn)-OH
Ac-EESVP-nV-(CO)-G-OH (SEQ ID NO: 28)	step IV: used Fmoc-Ser(tBu)-OH
Ac-EAVVP-nV-(CO)-G-OH (SEQ ID NO: 29)	Step V: used Fmoc-Ala-OH
Ac-EEHVP-nV-(CO)-G-OH (SEQ ID NO: 30)	step IV: used Fmoc-His(Trt)-OH
Ac-EENVP-nV-(CO)-G-OH (SEQ ID NO: 31)	step IV: used Fmoc-Asn(Trt)-OH
Ac-EEVV-P(4t-Ph)-nV-(CO)-G-OH (SEQ ID NO: 32)	step II: used Boc-Pro(4t-Ph)-OH
Ac-EEVV-P(3t-Me)-nV-(CO)-G-OH (SEQ ID NO: 33)	step II: used Boc-Pro(3t-Me)-OH
Ac-EE-Orn-VP-nV-(CO)-G-OH (SEQ ID NO: 34)	step IV: used Fmoc-Orn(Boc)-OH
Ac-EdEVVP-nV-(CO)-G-OH (SEQ ID NO: 35)	step V: used Fmoc-dGlu(OtBu)-OH
Ac-EE-(s,s)alloT-VP-nV-(CO)-G-	step IV: used Fmoc-(s,s)allo-Thr-OH

OH (SEQ ID NO: 36)	
Ac-EE-Dif-VP-nV-(CO)-G-OH (SEQ ID NO: 37)	step III: used Fmoc-Dif-OH
Ac-EE-daba-VP-nV-(CO)-G-OH (SEQ ID NO: 38)	step III: used Fmoc-*Daba(Boc)-OH
Ac-EEDVP-nV-(CO)-G-OH (SEQ ID NO: 39)	step IV: used Fmoc-Asp(OtBu)-OH
Ac-EEEVP-nV-(CO)-G-OH (SEQ ID NO: 40)	step IV: used Fmoc-Glu(OtBu)-OH
Ac-EETVP-nV-(CO)-G-OH (SEQ ID NO: 41)	step IV: used Fmoc-Thr(tBu)-OH
Ac-AEVVP-nV-(CO)-G-OH (SEQ ID NO: 42)	step VI: used Fmoc-Ala-OH
Ac-EELVP-nV-(CO)-G-OH (SEQ ID NO: 43)	step IV: used Fmoc-Leu-OH

*Note: Daba denotes diaminobutyric acid - -

(6) Please replace the title of Example II, at the top of page 110, with:

- - **Example II: Solution Phase Synthesis of Ac-EEVVP-nV-(CO)-G-allylAm** (SEQ ID NO: 44) - -

(7) Please replace the title of Step III, at the bottom of page 110, with:

- - **Step III.** Synthesis of Ac-Glu(OtBu)-Glu(OtBu)-Val-Val-Pro-OH (SEQ ID NO:45) (steps a-f below)- -

(8) Please replace page 111 with:

- -111

dimethylformamide (213 mL). Fmoc-Val-OH (1.5 g, 32 mmol) was coupled for four hours according to Procedure A. A small aliquot was taken for colorimetric

ninhydrin analysis which showed a 99.5% coupling efficiency in the production of the title compound.

b) Synthesis of Fmoc-Val-Val-Pro-2ClTrt resin

The resin from the previous step (0.53 mmol/g) was deprotected according to Procedure C. It was then coupled to Fmoc-Val-OH (10.85 g, 32 mmol) according to Procedure A with 99.5% efficiency.

c) Synthesis of Fmoc-Glu(OtBu)-Val-Val-Pro-2ClTrt resin (SEQ ID NO: 46)

The resin from the previous step (0.504 mmol/g) was deprotected according to Procedure C. It was then coupled to Fmoc-Glu(OtBu)-OH (13.63 g, 32 mmol) according to Procedure A with 99.4% efficiency.

d) Synthesis of Fmoc-Glu(OtBu)-Glu(OtBu)-Val-Val-Pro-2ClTrt resin (SEQ ID NO: 47)

The resin from the previous step (0.461 mmol/g) was deprotected according to Procedure C. It was then coupled to Fmoc-Glu(OtBu)-OH (13.63 g, 32 mmol) according to procedure A with 99.2% efficiency to yield the titled compound.

e) Synthesis of Ac-Glu(OtBu)-Glu(OtBu)-Val-Val-Pro-2ClTrt resin (SEQ ID NO: 48)

The resin from the previous step (0.42 mmol/g) was deprotected according to procedure C. The N-terminus was then capped according to Procedure D to yield the desired compound in 99.7% efficiency.

f) Synthesis of Ac-Glu(OtBu)-Glu(OtBu)-Val-Val-Pro-OH (SEQ ID NO: 49)

The resin from the previous step was transferred to a 1L plastic bottle and cleaved in the presence of 525 ml solution of acetic acid: trifluoroethanol: dichloromethane (1:1:3) with vigorous shaking for two hours. The resin was filtered using a fritted funnel and washed 3 × 50 mL with dichloromethane. The brownish red filtrate was concentrated to an oil which was then treated three times with 50 ml of a 1:1 mixture of dichloromethane: n-heptane. The crude off-white powder (13 g) was then dissolved in minimum amount of methanol and purified by HPLC using a 2.2 X 25 cm reverse phase column, containing a C-18 resin comprised of 10 micron size gel particles with a 300 angstrom pore size,

eluting with a gradient ranging from 15-55% acetonitrile in water. The pure fractions were - -

(9) Please replace the first full paragraph of page 112 with:

- - **Step IV.** Synthesis of Ac-Glu(OtBu)-Glu(OtBu)-Val-Val-Pro-nVal(CHOH)-Gly-OEt (SEQ ID NO: 50)

The compound of step III above (Ac-Glu(OtBu)-Glu(OtBu)-Val-Val-Pro-OH) (0.72 g, 1 mmol) was coupled to the compound of step II above (HCl•H-nVal(CHOH)-Gly-OEt) (0.27 g, 1 mmol) using HOAt (0.204 g, 1.5 mmol), HATU (0.418 g, 1.1 mmol) and diisopropylethylamine (0.87 mL, 5 mmol) in DMF at room temperature. After 18 hours, the reaction mixture was concentrated. The remaining residue was picked up in ethylacetate and washed three times each with 10 mL portions of 1N sodium bisulfate, saturated sodium bicarbonate and brine. It was then dried over sodium sulfate and concentrated to a crusty yellowish product which was taken to the next step without further purification (0.98 g). Analytical HPLC using a 4.6 X 250 mm reverse phase column, containing a C-18 resin comprised of 5 micron size gel particles with a 300 angstrom pore size, eluting with 5-50% acetonitrile (containing 0.1% trifluoroacetic acid) showed a 2:1 ratio of diastereomers with retention times of 21 minutes and 21.5 minutes, respectively. - -

(10) Please replace the second full paragraph of page 112 with:

- - **Step V.** Synthesis of Ac-Glu(OtBu)-Glu(OtBu)-Val-Val-Pro-nVal(CHOH)-Gly-OH (SEQ ID NO: 51)

To the compound obtained in step IV above (0.94 g, 1 mmol) in ethanol (15 mL) was added 1N lithium hydroxide (4 mL, 4 mmol) and the reaction was stirred at room temperature for two hours. The reaction was stopped by the addition of enough Dowex ion exchange resin (50 X8-400) to obtain an acidic solution, pH ~3. After stirring for 15 minutes, the reaction mixture was filtered and concentrated. The crude product was subjected to HPLC purification using a 5.5 X 30 cm reverse phase column, containing a C-18 resin comprised of 5 micron

size gel particles with a 300 angstrom pore size, eluting with a 30 minute gradient using 5-30% acetonitrile in water. The desired fractions were pulled and concentrated to a white solid (238 mg, 26%). - -

(11) Please replace page 113 with:

Step VI. Synthesis of Ac-Glu(OtBu)-Glu(OtBu)-Val-Val-Pro-nVal(CHOH)-Gly-allylamide (SEQ ID NO: 52)

The compound of step V above (129 mg, 0.14 mmol) was coupled to allylamine (13 l, 0.17 mmol) in the presence of HOBt (58.5 mg, 0.38 mmol), EDC (54.3 mg, 0.28 mmol) and diisopropylethylamine (124 l, 0.71 mmol) in dimethylformamide (10 ml). After 18 hours, the reaction mixture was concentrated and the remaining residue was picked-up in ethylacetate and washed three times each with 5 mL portions of 1N sodium bisulfate, saturated sodium bicarbonate and brine. After drying over sodium sulfate, the organic layer was concentrated to give a white precipitate which was taken to the next step without further purification (115 mg, 85%). Analytical HPLC using a 4.6 X 250 mm reverse phase column, containing a C-18 resin comprised of 5 micron size gel particles with a 300 angstrom pore size, eluting with 5-50% acetonitrile (containing 0.1% trifluoroacetic acid) showed two diastereomeric peaks with retention times of 15.9 and 16.5 minutes, respectively. Low resolution mass spectrum confirmed the desired mass (M + Na^+ 973.5).

Step VII. Synthesis of Ac-Glu(OtBu)-Glu(OtBu)-Val-Val-Pro-nVal(CO)-Gly-allylamide (SEQ ID NO: 53)

Under a stream of nitrogen gas, the product of step VI above (115.2 mg, 0.12 mmol) was dissolved in dimethylsulfoxide (5 mL) and toluene (5 mL). Water soluble carbodiimide (EDC, 232.2 mg, 1.21 mmol) was then added in one batch. The reaction mixture was cooled to 0°C and dichloroacetic acid (52 l, 0.60 mmol) was added dropwise. Stirring at 0°C continued for 15 minutes. The ice bath was removed and the reaction continued for two hours at room temperature. The toluene was removed under reduced pressure. The remaining solution was

diluted with ethylacetate and washed three times each with 5 mL portions of 1N sodium bisulfate, saturated sodium bicarbonate and brine. It was then concentrated to a yellowish foam (85.5 mg, 74.4%).

Step VIII. Synthesis of Ac-Glu-Glu-Val-Val-Pro-nVal(CO)-Gly-allylamide (SEQ ID NO: 54)

The product of step VII above (0.86 g, 0.91 mmol) was treated with a 1:1 mixture of dichloromethane: trifluoroacetic acid (20 ml) for one hour. The reaction mixture was then concentrated and the remaining residue was purified using a

2.2 - -

(12) Please replace page 114 with:

- -114

X 25 cm reverse phase HPLC column, containing a C-18 resin comprised of 10 micron size gel particles with a 300 angstrom pore size, eluting with a 30 minutes gradient using 10-25% acetonitrile in water. The purified fractions were pulled and lyophilized to a white powder (21.5 mg, 28.5%). Analytical HPLC using a 4.6 X 250 mm reverse phase column, containing a C-18 resin comprised of 5 micron size gel particles with a 300 angstrom pore size, eluting with 5-75% acetonitrile (containing 0.1% trifluoroacetic acid) showed one peak at 9.5 minutes. Low resolution mass spectrum confirmed the desired mass (MH^+ 837.5).

Table of Compounds synthesized according to Example II

COMPOUND NAME	SYNTHESIS
Ac-EEVVP-nV-(CO)-G-allylAm (SEQ ID NO: 55)	example II
Ac-EEVVP-nV-(CO)-G-2PhEtAm (SEQ ID NO: 56)	step VI: used phenethylamine
Ac-EEVVP-nV-(CO)-G-PropAm (SEQ ID NO: 57)	step VI: used propylamine
Ac-EEVVP-nV-(CO)-G-propynylAm	step VI: used

(SEQ ID NO: 58)	propynylamine
Ac-EEVVP-nV-(CO)-G-iPrAm (SEQ ID NO: 59)	step VI: used isopropylamine

- -

(13) Please replace the title of Example III, at the top of page 115, with:

- - **Example III: Solution Phase Synthesis of Ac-EEVVP-nV-(CO)-G(Oallyl)** (SEQ ID NO: 60) - -

(14) Please replace the title of Step III, at the bottom of page 117, with:

- - **Step III.** Synthesis of Ac-Glu(OtBu)-Glu(OtBu)-Val-Val-Pro-nVal(CHOH)-Gly-Oallyl (SEQ ID NO: 61) - -

(15) Please replace the first full paragraph of page 118 with:

- - **Step IV.** Synthesis of Ac-Glu(OtBu)-Glu(OtBu)-Val-Val-Pro-nVal(CO)-Gly-Oallyl (SEQ ID NO: 62)

Under a stream of nitrogen gas, the product of the previous step (51.5 mg, 0.054 mmol) was dissolved in dimethylsulfoxide (1.2 mL) and toluene (1.2 mL). Water soluble carbodiimide (EDC, 103.8 mg, 0.54 mmol) was then added in one batch. The reaction mixture was cooled to 0°C and dichloroacetic acid (22.3 l, 0.27 mmol) was added dropwise. Stirring at 0°C continued for 15 minutes. The ice bath was removed and the reaction was slowly brought to room temperature. The reaction was stopped after 90 minutes. The toluene was removed under reduced pressure. The reaction was diluted with ethylacetate and washed with 1N sodium bisulfate, saturated sodium bicarbonate and brine. It was then concentrated to a yellowish foam (40.4 mg, 79%) and taken to the next step without further purification.- -

(16) Please replace the second full paragraph of page 118 with:

- - **Step V.** Synthesis of Ac-Glu-Glu-Val-Val-Pro-nVal(CO)-Gly-Oallyl (SEQ ID NO: 63)

The product of the previous step (40.4 mg, 0.042 mmol) was treated with a 1:1 mixture of dichloromethane: trifluoroacetic acid (4 mL) for two hours. The reaction mixture was then concentrated and purified on a 1 X 25 cm reverse phase HPLC column, containing a C-18 resin comprised of 10 micron size gel particles with a 300 angstrom pore size, eluting with a 30 minute gradient using 10-30% acetonitrile in water. The desired fractions were pulled and concentrated to a white powder (8.5 mg, 24%). Analytical HPLC using a 4.6 X 250 mm reverse phase column, containing a C-18 resin comprised of 5 micron size gel particles with a 300 angstrom pore size, ran at 5-50% acetonitrile (containing 0.1% trifluoroacetic acid) showed one peak at 15 minutes. Low resolution mass spectrum confirmed the desired mass (MH^+ 838.O).- -

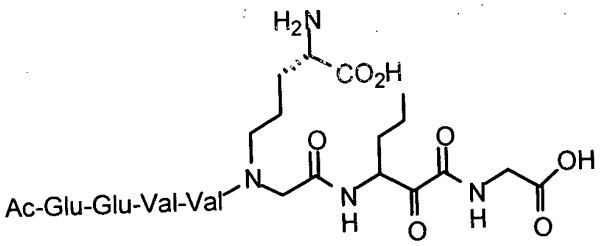
(17) Please replace page 119 with:

Table: Compounds synthesized according to Example III

COMPOUND NAME	SYNTHESIS
Ac-EEVVPnV-(CO)-G-Oallyl (SEQ ID NO: 64)	example III
Ac-EEVVP-nL-(CO)-G-Oallyl (SEQ ID NO: 65)	step I(b1): used Fmoc-nLeu-OH
Ac-EEVVP-V-(CO)-G-Oallyl (SEQ ID NO: 66)	step I(b1): used Fmoc-Val-OH
Ac-EEVVPL-(CO)-G-Oallyl (SEQ ID NO: 67)	step I(b1): used Fmoc-Leu-OH
Ac-EEVVP-G(propynyl)-(CO)-G-Oallyl(SEQ ID NO: 68)	step I(b1): used Fmoc-Gly(propynyl)-OH
Ac-EEVVPnV-(CO)-G-OEt (SEQ	step Ic: used ethyl isocyanoacetate

ID NO: 69)	
Ac-EEVVP-G(allyl)-(CO)-G-Oallyl (SEQ ID NO: 70)	step I(b1): used Fmoc-Gly(allyl)-OH
Ac-EEVVG-L-(CO)-G-Oallyl (SEQ ID NO: 71)	step I(b1): used Fmoc-Leu-OH, example II, step IIIa: used Gly-2ClTrt-resin
Ac-EEVVPnV-(CO)-G-OtBu (SEQ ID NO: 72)	step Ic: used t-butyl isocyanoacetate
Ac-EEVVP-G(allyl)-(CO)-G-OEt (SEQ ID NO: 73)	step Ic: used ethyl isocyanoacetate, step I(b1): used Fmoc-Gly(allyl)-OH
Ac-EEVVP-C(Me)-(CO)-G-OMe (SEQ ID NO: 74)	step Ic: used methyl isocyanoacetate, step I(b1): used Boc-Cys(Me)-OH

Example IV: Solid Phase Synthesis of Ac-EEVV-G(N-Bu(4NH2,4-CO2H))-nV-(CO)-G-OH (SEQ ID NO: 75)



Step I. Synthesis of bromoacetyl-nVal(dpsc)-Gly-PAM resin

(18) Please replace the title of Step III, at the bottom of page 120, with:

Step III. Synthesis of Ac-Glu-Glu-Val-Val-Gly(N-Bu(4NH2,4-COOH)-nVal(CO)-Gly-OH (SEQ ID NO: 76)

(19) Please replace page 121 with:

-121

c) The resin was deprotected according to Procedure C and coupled to Fmoc-Glu(OtBu)-OH (0.04 g, 0.10 mmol) according to Procedure B.

d) The resin was deprotected according to Procedure C and coupled to Fmoc-Glu(OtBu)-OH (0.04 g, 0.10 mmol) according to Procedure B.

e) The resin was deprotected according to Procedure C and acylated at the N-terminus according to Procedure E.

f) The semicarbazone group of the product obtained in step e was hydrolyzed according to Procedure F, and the product was subjected to HF cleavage according to Procedure G. The crude material was subjected to HPLC purification using a 1 X 25 cm reverse phase column, containing a C-18 resin comprised of 10 micron size gel particles with a 300 angstrom pore size, eluting with a 30 minute gradient using 10-40% acetonitrile in water. Analytical HPLC using a 4.6 X 250 mm reverse phase column, containing a C-18 resin comprised of 5 micron size gel particles with a 300 angstrom pore size, eluting with 5-75% acetonitrile (containing 0.1% trifluoroacetic acid) showed one peak at 8 minutes. Low resolution mass spectrum confirmed the presence of the desired product (MH^+ 873.5).

Table of Compounds synthesized according to Example IV

COMPOUND NAME	SYNTHESIS
Ac-EEVV-G(N-Bu(4NH2,4-CO2H))-nV-(CO)-G-OH (SEQ ID NO: 77)	example IV
Ac-EEVV-G(N-Et(CO2H))-nV-(CO)-G-OH (SEQ ID NO: 78)	step II: used -Ala(OtBu)•HCl
Ac-EEVV-G(N-EtPh(3,4diOMe))-nV-(CO)-G-OH (SEQ ID NO: 79)	step II: used 3,4-dimethoxyphenethylamine
Ac-EEVV-G(N-Pe(5-NH2,5-CO2H))-nV-(CO)-G-OH (SEQ ID NO: 80)	step II: used CBz-Lys(OBzl)•benzene sulfonate

Example V: Solid Phase Synthesis of Ac-EEVV-G(N-Et(NHBz))-nV-(CO)-G-OH (SEQ ID NO: 81)

- -

(20) Please replace the title of Step II, at the bottom of page 122, with:

- - **Step II.** Synthesis of Fmoc-Val-Gly(N-Et(NH-Boc))-nVal(dpsc)-Gly-PAM resin (SEQ ID NO: 82)- -

(21) Please replace the title of Step III, at the bottom of page 122, with:

- - **Step III.** Synthesis of Fmoc-Val-Gly(N-Et(NHBz))-nVal(dpsc)-Gly-PAM resin (SEQ ID NO: 83)- -

(22) Please replace the title of Step IV, at the top of page 123, with:

- - **Step IV.** Synthesis of Ac-Glu-Glu-Val-Val-Gly(N-Et(NHBz))-nVal(CO)-Gly-OH (SEQ ID NO: 84) - -

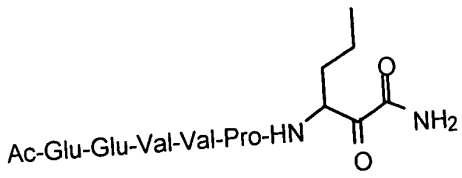
(23) Please replace page 124 with:

- -124

Table of Compounds synthesized according to Example V

COMPOUND NAME	SYNTHESIS
Ac-EEVV-G(N-Et(NHBz))-nV-(CO)-G-OH (SEQ ID NO: 84)	example V
Ac-EEVV-G(N-Et(NHBzl(3-OPh)))-nV-(CO)-G-OH (SEQ ID NO: 85)	step III: used 3-phenoxybenzoic acid as capping group
Ac-EEVV-G(N-Prop(NHBz))-nV-(CO)-G-OH (SEQ ID NO: 86)	step I: used t-butyl N-(2-aminopropyl)-carbamate

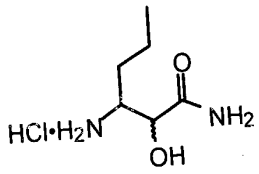
Example VI: Solid Phase Synthesis of Ac-EEVVP-nV(CO)-Am (SEQ ID NO: 87)



Step I. Formation of HOBt ammonium salt

Ammonium hydroxide (0.5 mL) was added dropwise to a slurry of HOBt (2 g, 13.07 mmol) in water (5 mL). The mixture was stirred at room temperature until a clear solution was obtained. The product was precipitated by the slow addition of acetone (50 mL). It was then filtered on a glass funnel and washed thoroughly with cold acetone (white powder, 2.23 g, 78%; mp 177-181°C).

Step II. Synthesis of HCl•H-nVal-(CHOH)-CONH2



Boc-nVal-(CHOH)-COOH (295 mg, 1.19 mmol) (example V, step II) was reacted with the product of the previous step (362 mg, 2.38 mmol) in the presence of EDC (342 mg, 1.78 mmol) in dimethylformamide (10 mL) at room temperature for 18 hours. The reaction mixture was concentrated and the remaining residue was picked up in ethylacetate (5 mL) and washed three times each with 5 mL portions of 1N sodium bisulfate, saturated sodium bicarbonate and brine. The organic layer was dried over sodium sulfate and concentrated to a white solid (170 - -

(24) Please replace the first full paragraph of page 125 with:

- - **Step III.** Synthesis of Ac-Glu(OtBu)-Glu(OtBu)-Val-Val-Pro-nVal-(CHOH)-CONH2 (SEQ ID NO: 88)

The product obtained from step II above (19 mg, 0.103 mmol) was coupled to Ac-Glu(OtBu)-Glu(OtBu)-Val-Val-Pro-OH (example II, step IIIf) (50 mg, 0.069 mmol) in the presence of HOAt (14.1 mg, 0.103 mmol), HATu (28.8

mg, 0.076 mmol), diisopropylethylamine (60 µl, 0.345 mmol) in dimethylformamide (10 mL) for 4 hours at room temperature. The DMF was removed under reduced pressure and the remaining residue was picked up in ethylacetate and washed with 1N sodium bisulfate, saturated sodium bicarbonate and brine. After drying over sodium sulfate it was concentrated to give a white solid (40 mg, 68%) which was taken to the next step without further purification. Low resolution mass spectrum confirmed the desired mass (M + Na^+ 876.5).- -

(25) Please replace the second full paragraph of page 125 with:

- - **Step IV.** Synthesis of Ac-Glu(OtBu)-Glu(OtBu)-Val-Val-Pro-nVal-(CO)-CONH2 (SEQ ID NO: 89)

Under a stream of nitrogen gas, the product of the previous step (40 mg, 0.047 mmol) was dissolved in dimethylsulfoxide (4 mL) and toluene (4 mL). Water soluble carbodiimide (EDC, 89.8 mg, 0.47 mmol) was then added in one batch. The reaction mixture was cooled to 0°C and dichloroacetic acid (20 l, 0.23 mmol) was added dropwise. Stirring at 0°C continued for 15 minutes. The ice bath was removed and the reaction was slowly brought to room temperature. The reaction was stopped after 90 minutes. The toluene was removed under reduced pressure. The reaction was diluted with ethylacetate and washed with 1N sodium bisulfate, saturated sodium bicarbonate and brine. It was then concentrated to a yellowish foam (40 mg, 53%) and taken to the next step without further purification. Low resolution mass spectrum confirmed the desired mass (M + Na^+ 852.5).- -

(26) Please replace page 126 with:

- -126

Step V. Synthesis of Ac-Glu-Glu-Val-Val-Pro-nVal-(CO)-CONH2 (SEQ ID NO:90)

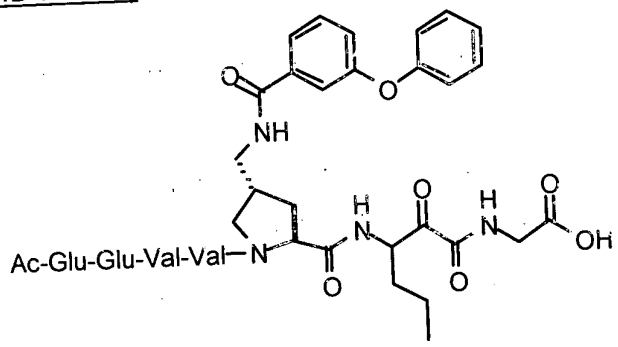
The product of the previous step (39.9 mg, 0.047 mmol) was treated with a 1:1 mixture of dichloromethane: trifluoroacetic acid (10 mL) for two hours. The reaction mixture was concentrated and the remaining residue was subjected to

HPLC purification using a 1 X 25 cm reverse phase column, containing a C-18 resin comprised of 10 micron size gel particles with a 300 angstrom pore size, eluting with a 30 minute gradient using 5-25% acetonitrile in water. The purified fractions were pulled and lyophilized to a white powder (3.6 mg, 10%). Low resolution mass spectrum confirmed the desired mass (MH^+ 740.O).

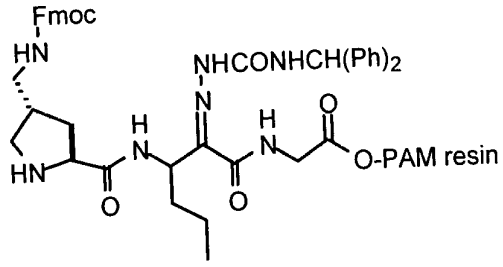
Table of Compounds synthesized according to Example VI

COMPOUND NAME	SYNTHESIS
Ac-EEVVP-nV-(CO)-Am (SEQ ID NO:91)	example VI

Example VII: Solid Phase Synthesis of Ac-EEVV-P(4t-MeNHBzl(3-OPh))-nV-(CO)-G-OH (SEQ ID NO:92)



Step I. Synthesis of H-Pro(4t-MeNHFmoc)-nVal-(dpsc)-Gly-PAM resin



The resin obtained from example I (step I) (0.70 g, 0.36 mmol) was coupled with Boc-Pro(4t-MeNHFmoc)-OH according to procedure B for 18 hours, with- -

(27) Please replace the title of Step II, at the top of page 127, with:

- - **Step II.** Synthesis of Ac-Glu(OtBu)-Glu(OtBu)-Val-Val -Pro(4t-MeNHFmoc)-nVal-(dpsc)-Gly-PAM resin (SEQ ID NO: 93)- -

(28) Please replace the title of Step III, at the top of page 127, with:

- - **Step III.** Synthesis of Ac-Glu(OtBu)-Glu(OtBu)-Val-Val-Pro(4t-MeNH2)-nVal-(dpsc)-Gly-PAM resin (SEQ ID NO: 94)- -

(29) Please replace the title of Step IV, in the middle of page 127, with:

- - **Step IV.** Synthesis of Ac-Glu(OtBu)-Glu(OtBu)-Val-Val -Pro(4t-MeNHBzl(3-OPh))-nVal-(dpsc)-Gly-PAM resin (SEQ ID NO: 95)- -

(30) Please replace the title of Step V, at the bottom of page 127, with:

- - **Step V.** Synthesis of Ac-Glu-Glu-Val-Val-Pro(4t-MeNHBzl(3-OPh))-nVal-(CO)-Gly-OH (SEQ ID NO: 96)- -

(31) Please replace page 128 with:

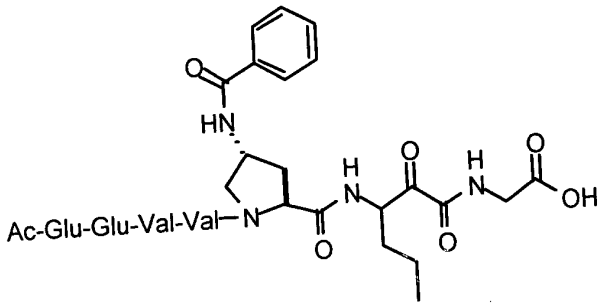
with 5-75% acetonitrile (containing 0.1% trifluoroacetic acid) showed one peak at 14.5 minutes. Low resolution mass spectrum confirmed the presence of the desired product (MH^+ 1049.5).

Table of Compounds synthesized according to Example VII

COMPOUND NAME	SYNTHESIS
Ac-EEVV-P(4t-MeNHBzl(3-OPh))-nV-(CO)-G-OH (SEQ ID NO: 92)	example VII
Ac-EEVV-P(4t-MeNHCO2Ph)-nV-(CO)-G-OH (SEQ ID NO: 97)	step IV: used phenyl chloroformate, DIEA, NMP
Ac-EEVV-P(4t-MeNHCOPh)-nV-(CO)-G-OH (SEQ ID NO: 98)	step IV: used benzoyl chloride, DIEA, NMP
Ac-EEVV-P(4t-MeNH-Fmoc)-nV-(CO)-G-OH (SEQ ID NO: 99)	omitted steps III and IV

Ac-EEVV-P(4t-MeNHSO2Ph)-nV-(CO)-G-OH (SEQ ID NO: 100)	step IV: used benzenesulfonyl chloride, 2,4,6-collidine, NMP
Ac-EEVV-P(4t-MeUreaPh)-nV-(CO)-G-OH (SEQ ID NO: 101)	step IV: used phenyl isocyanate, DIEA, NMP
Ac-EEVV-P(4t-NH-Fmoc)-nV-(CO)-G-OH (SEQ ID NO: 102)	step I: used Boc-Pro(4t-NH-Fmoc)-OH

Example VIII: Solid Phase Synthesis of Ac-EEVV-P(4t-NHBZl)-nV-(CO)-G-OH (SEQ ID NO: 103)



Step I. Synthesis of Boc-Pro(4t-NH2)-nVal-(dpsc)-Gly-PAM resin - -

(32) Please replace the title of Step III, at the bottom of page 129, with:

- - **Step III.** Synthesis of Fmoc-Val-Pro(4t-NHBzl)-nVal-(dpsc)-Gly-PAM resin (SEQ ID NO: 104) - -

(33) Please replace the title of Step IV, at the bottom of page 129, with:

- - **Step IV.** Synthesis of Fmoc-Val-Val-Pro(4t-NHBzl)-nVal-(dpsc)-Gly-PAM resin (SEQ ID NO: 105)- -

(34) Please replace page 130 with:

- -130

solution showing a high yield for the deprotection. The resin was resuspended in N-methylpyrrolidine (1.47 mL) and was coupled to Fmoc-Val-OH (0.03, 0.10 mmol) as in step III.

Step V. Synthesis of Fmoc-Glu(OtBu)-Val-Val-Pro(4t-NHBzl)-nVal-(dpsc)-Gly-PAM resin (SEQ ID NO: 106)

The compound of the previous step (100 mg, 0.03 mmol) was deprotected according to Procedure D. A ninhydrin assay on a small aliquot gave dark blue resin and solution showing a high yield for the deprotection. The resin was resuspended in N-methylpyrrolidine (1.47 mL) and was coupled to Fmoc-Glu(OtBu)-OH (0.04 g, 0.10 mmol), according to Procedure B for 5 hours. A small aliquot was taken for qualitative ninhydrin analysis which showed colorless beads and solution indicating a high yield of coupling.

Step VI. Synthesis of Fmoc-Glu(OtBu)-Glu(OtBu)-Val-Val-Pro(4t-NHBzl)-nVal-(dpsc)-Gly-PAM resin (SEQ ID NO: 107)

The compound of the previous step (100 mg) was deprotected according to Procedure D and coupled to Fmoc-Glu(OtBu)-OH (0.04 g, 0.10 mmol) in the same manner.

Step VII. Synthesis of Ac-Glu-Glu-Val-Val-Pro(4t-NHBzl)-nVal-(CO)-Gly-OH (SEQ ID NO: 108)

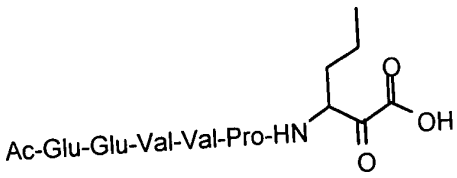
The compound of previous step (100 mg) was deprotected according to Procedure C and acylated according to Procedure E. The resin was vacuum dried and a small aliquot was taken for qualitative ninhydrin analysis which showed colorless beads and solution indicating a high yield of coupling. The resin was then subjected to semicarbazone hydrolysis followed by HF cleavage reactions according to Procedures F and H, respectively. The crude product was subjected to HPLC purification using a 1 X 25 cm reverse phase column, containing a C-18 resin comprised of 10 micron size gel particles with a 300 angstrom pore size, eluting with a 30 minute gradient using 10-40% acetonitrile in water. Analytical HPLC using a 4.6 X 250 mm reverse phase column, containing a C-18 resin comprised of 5 micron size gel particles with a 300 angstrom pore size, ran at 5-50% acetonitrile (containing 0.1% trifluoroacetic acid) showed one peak at 13 minutes. Low resolution mass spectrum confirmed the presence of the desired product (MH^+ 917.5). - -

(35) Please replace page 131 with:

Table of Compounds synthesized according to Example VIII

COMPOUND NAME	SYNTHESIS
Ac-EEVV-P(4t-NHBzl)-nV-(CO)-G-OH (SEQ ID NO: 103)	example VIII
Ac-EEVV-P(4t-NHBzl(4-OMe))-nV-(CO)-G-OH (SEQ ID NO: 109)	step II: used 4-methoxybenzoyl chloride, DIEA, NMP
Ac-EEVV-P(4t-NHBzl(4-OPh))-nV-(CO)-G-OH (SEQ ID NO: 110)	step II: used 4-phenoxybenzoic acid
Ac-EEVV-P(4t-NHBzl(3-OPh))-nV-(CO)-G-OH (SEQ ID NO: 111)	step II: used 3-phenoxybenzoic acid
Ac-EEVV-P(4t-NHBzl(3,4-OMeO))-nV-(CO)-G-OH (SEQ ID NO: 112)	step II: used piperonyloyl chloride, DIEA, NMP
Ac-EEVV-P(4t-NHBzl(4F))-nV-(CO)-G-OH (SEQ ID NO: 113)	step II: used 4-fluorobenzoyl chloride, DIEA, NMP
Ac-EEVV-P(4t-NHiBoc)-nV-(CO)-G-OH (SEQ ID NO: 114)	step II: used isobutyl chloroformate, DIEA, NMP
Ac-EEVV-P(4t-NHSO2Ph)-nV-(CO)-G-OH (SEQ ID NO: 115)	step II: used benzene sulfonyl chloride, 2,4,6-collidine, NMP
Ac-EEVV-P(4t-NHSO2Ph(4-OMe))-nV-(CO)-G-OH (SEQ ID NO: 116)	step II: used 4-methoxybenzene sulfonyl chloride, 2,4,6-collidine, NMP
Ac-EEVV-P(4t-UreaPh)-nV-(CO)-G-OH (SEQ ID NO: 117)	step II: used phenyl isocyanate, DIEA, NMP
Ac-EEVV-P(4t-UreaPh(4-OMe))-nV-(CO)-G-OH (SEQ ID NO: 118)	step II: used 4-methoxyphenyl isocyanate, DIEA, NMP

Example IX: Solution Phase Synthesis of Ac-EEVVP-nV-(CO)-OH (SEQ ID NO: 119)



Step I. Synthesis of ethyl (R,S)-2-hydroxy-3-amino hexanoate hydrochloride - -

(36) Please replace the title of Step II, at the top of page 132, with:

- - **Step II.** Synthesis of Ac-Glu(OtBu)-Glu(OtBu)-Val-Val-Pro-nVal(CHOH)-OEt (SEQ ID NO:120) - -

(37) Please replace the title of Step III, at the bottom of page 132, with:

- - **Step III.** Synthesis of Ac-Glu(OtBu)-Glu(OtBu)-Val-Val-Pro-nVal(CHOH)-carboxylic acid (SEQ ID NO: 121)- -

(38) Please replace page 133 with:

- - 133

X8-400) to obtain an acidic solution, pH ~3. After stirring for 15 minutes, the reaction mixture was filtered and concentrated to a white solid (53.4 mg, 82.2%).

Step IV. Synthesis of Ac-Glu-Glu-Val-Val-Pro-nVal(CHOH)-carboxylic acid (SEQ ID NO: 122)

The product obtained in the previous step (53.1 mg) stirred in a 1:1 mixture of trifluoroacetic acid: dichloromethane (10 mL) for 90 minutes. The reaction mixture was concentrated to a yellowish solid (50 mg) which was taken to the next step without further purification.

Step V. Synthesis of Ac-Glu-Glu-Val-Val-Pro-nVal(CO)-carboxylic acid (SEQ ID NO: 123)

The product obtained in the previous step (55.7 mg, 0.075 mmol) was dissolved in dichloromethane (8 mL) and dimethylsulfoxide (2 mL). Triethylamine (125.5 l, 0.901 mmol) followed by pyridine sulfur trioxide (143.4 mg, 0.901 mmol) were added and the reaction was stirred at room temperature for two

hours. Dichloromethane was removed under reduced pressure and the remaining residue was diluted with methanol (containing 0.1 % TFA) and purified on a reverse phase HPLC column (1 X 25 cm) containing a C-18 resin comprised of 10 micron size gel particles with a 300 angstrom pore size, eluting with a 30 minute gradient using 5-15% acetonitrile in water. The desired fractions were pulled and concentrated to an oil (15.2 mg, 27.4%). Analytical HPLC using a 4.6 X 250 mm reverse phase column, containing a C-18 resin comprised of 5 micron size gel particles with a 300 angstrom pore size, ran at 5-50% acetonitrile (containing 0.1% trifluoroacetic acid) showed one peak at 11 minutes. Low resolution mass spectrum confirmed the desired mass (MH^+ 741.0).

Table of Compound synthesized according to Example IX

Ac-EEVVP-nV-(CO)-OH (SEQ ID NO: 124)	example IX

Assay for HCV Protease Inhibitory Activity:

Spectrophotometric Assay: Spectrophotometric assay for the HCV serine protease was performed on the inventive compounds by following the procedure described by R. Zhang *et al*, *Analytical Biochemistry*, 270 (1999) 268-275, the disclosure of which is incorporated herein by reference. The assay based on the proteolysis of chromogenic ester substrates is suitable for the continuous monitoring of HCV NS3 protease activity. The substrates were derived from the P- -

(39) Please replace the first paragraph (partial) on page 134 with:

- -

side of the NS5A-NS5B junction sequence (Ac-DTEDVVX(Nva)(SEQ ID NO: 125), where X = A or P) whose C-terminal carboxyl groups were esterified with one of four different chromophoric alcohols (3- or 4-nitrophenol, 7-hydroxy-4-methyl-coumarin, or 4-phenylazophenol). Presented below are the synthesis, characterization and application of these novel spectrophotometric ester

substrates to high throughput screening and detailed kinetic evaluation of HCV NS3 protease inhibitors.- -

(40) Please replace page 136 with:

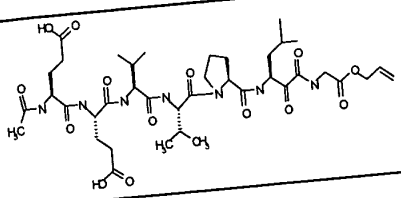
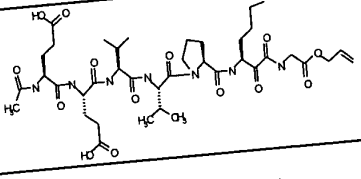
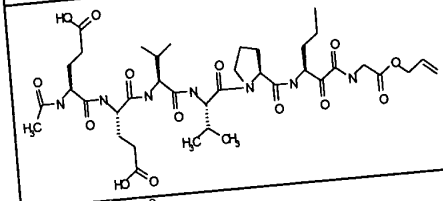
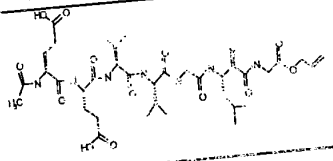
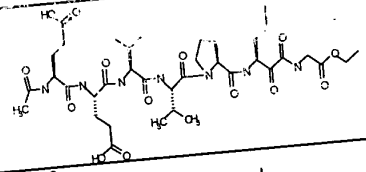
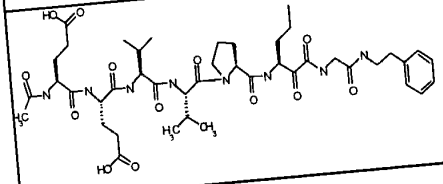
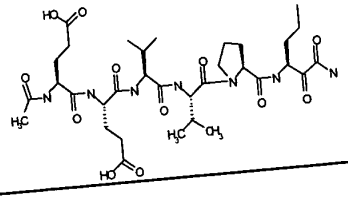
pH 6.5, 300 mM NaCl, 10% glycerol, 0.05% lauryl maltoside, 5 µM EDTA and 5 µM DTT) were optimized for the NS3/NS4A heterodimer (D. L. Sali *et al*, *ibid.*)). Typically, 150 µl mixtures of buffer, substrate and inhibitor were placed in wells (final concentration of DMSO 4 % v/v) and allowed to preincubate at 30 °C for approximately 3 minutes. Fifty µls of prewarmed protease (12 nM, 30°C) in assay buffer, was then used to initiate the reaction (final volume 200 µl).The plates were monitored over the length of the assay (60 minutes) for change in absorbance at the appropriate wavelength (340 nm for 3-Np and HMC, 370 nm for PAP, and 400 nm for 4-Np) using a Spectromax Plus microtiter plate reader equipped with a monochrometer (acceptable results can be obtained with plate readers that utilize cutoff filters). Proteolytic cleavage of the ester linkage between the Nva and the chromophore was monitored at the appropriate wavelength against a no enzyme blank as a control for non-enzymatic hydrolysis. The evaluation of substrate kinetic parameters was performed over a 30-fold substrate concentration range (~6-200 µM). Initial velocities were determined using linear regression and kinetic constants were obtained by fitting the data to the Michaelis-Menten equation using non-linear regression analysis (Mac Curve Fit 1.1, K. Raner). Turnover numbers (k_{cat}) were calculated assuming the enzyme was fully active.

Evaluation of Inhibitors and Inactivators: The inhibition constants (K_i) for the competitive inhibitors Ac-D-(D-Gla)-L-I-(Cha)-C-OH (27) (SEQ ID NO: 126), Ac-DTEDVVA(Nva)-OH (SEQ ID NO: 127) and Ac-DTEDVVP(Nva)-OH (SEQ ID NO: 128) were determined experimentally at fixed concentrations of enzyme and substrate by plotting v_o/v_i vs. inhibitor concentration ($[I]_o$) according to the rearranged Michaelis-Menten equation for competitive inhibition kinetics: $v_o/v_i = 1 + [I]_o/(K_i (1 + [S]_o/K_m))$, where v_o is the uninhibited initial velocity, v_i is the initial

velocity in the presence of inhibitor at any given inhibitor concentration ($[I]_o$) and $[S]_o$ is the substrate concentration used. The resulting data were fitted using linear regression and the resulting slope, $1/(K_i(1+[S]_o/K_m)$, was used to calculate the K_i^* value.

The obtained K_i^* values for the various compounds of the present invention are given in the **Tables** wherein the compounds have been arranged in the order of ranges of K_i^* values. From these test results, it would be apparent to the skilled - -

(41) Please replace page 138 with:- -

STRUCTURE	NAME	Ki* Range
	Ac-EEVVP-L-(CO)-G-Oallyl ~~(SEQ ID NO: 67)~~	
	Ac-EEVVP-nL-(CO)-G-Oallyl ~~(SEQ ID NO: 65)~~	a
	Ac-EEVVP-nV-(CO)-G-Oallyl ~~(SEQ ID NO: 64)~~	a
	Ac-EEVVG-L-(CO)-G-Oallyl ~~(SEQ ID NO: 71)~~	b
	Ac-EEVVT-nV-(CO)-G-OEt ~~(SEQ ID NO: 69)~~	c
	Ac-EEVVP-nV-(CO)-G-2PhEtAm ~~(SEQ ID NO: 56)~~	c
	Ac-EEVVP-nV-(CO)-Am ~~(SEQ ID NO: 91)~~	b

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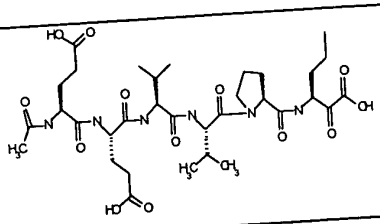
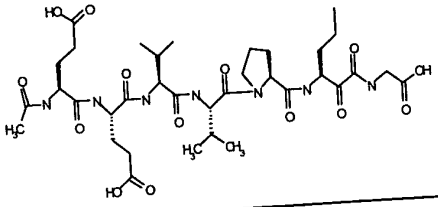
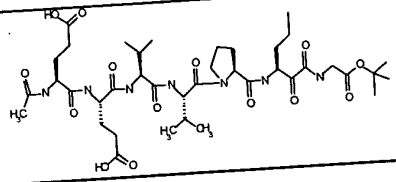
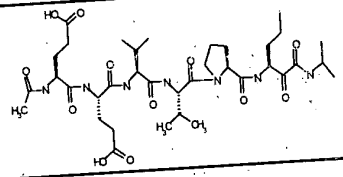
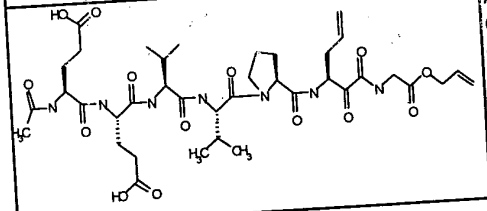
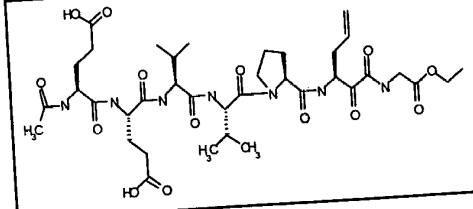
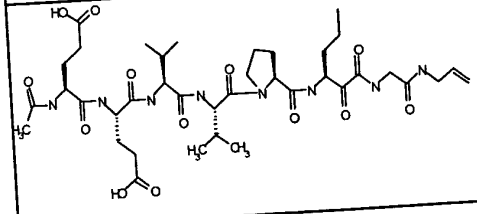
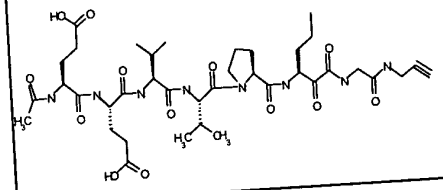
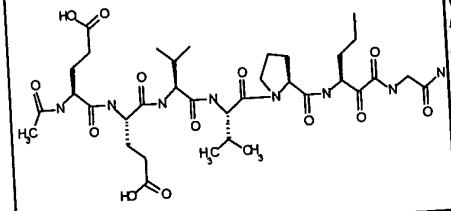
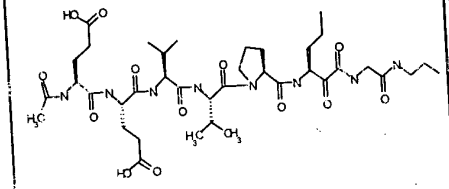
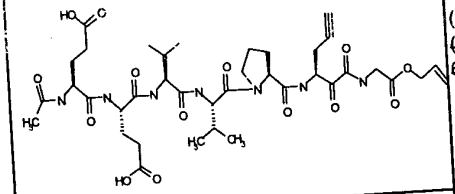
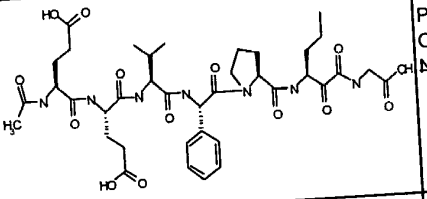
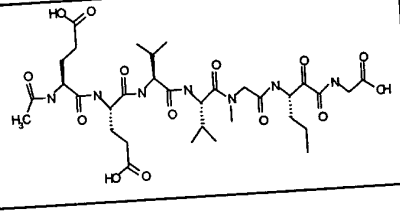
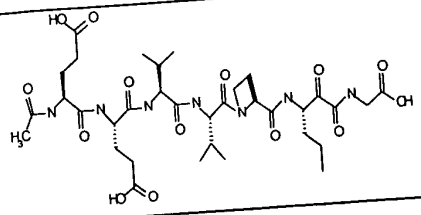
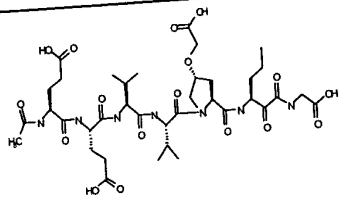
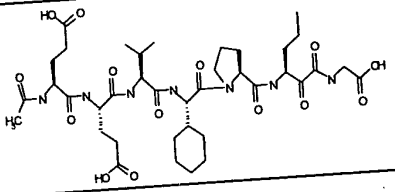
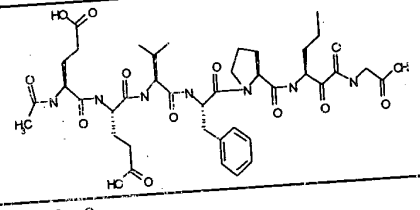
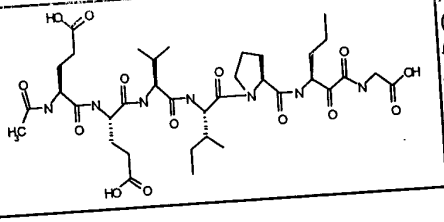
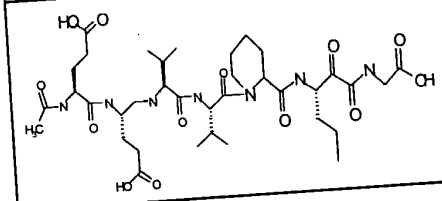
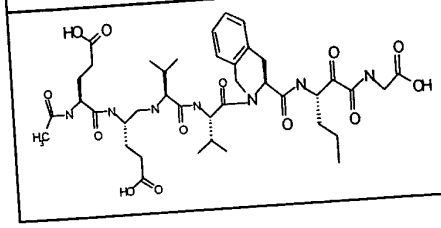
(42) Please replace page 139 with:

	Ac-EEVVP-nV-(CO)-OH ~~(SEQ ID NO: 119)~~	c
	Ac-EEVVP-nV-(CO)-G-OH ~~(SEQ ID NO: 9)~~	a
	Ac-EEVVP-nV-(CO)-G-OtBu ~~(SEQ ID NO: 72)~~	b
	Ac-EEVVP-nV-(CO)-iPrAm ~~(SEQ ID NO: 129)~~	c
	Ac-EEVVP-G(allyl)-(CO)-G-Oallyl ~~(SEQ ID NO: 70)~~	b
	Ac-EEVVP-G(allyl)-(CO)-G-OEt ~~(SEQ ID NO: 73)~~	b
	Ac-EEVVP-nV-(CO)-G-allylAm ~~(SEQ ID NO: 44)~~	b

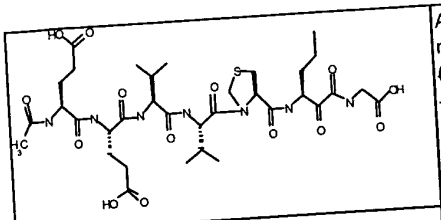
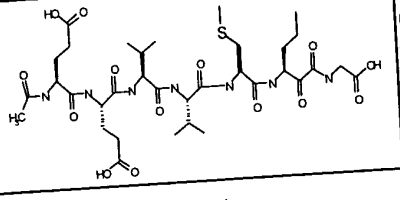
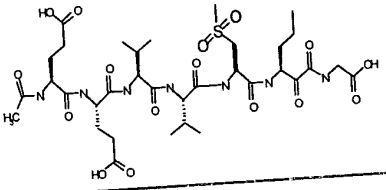
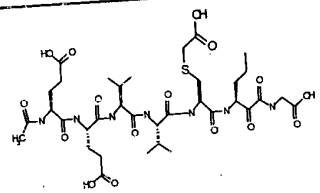
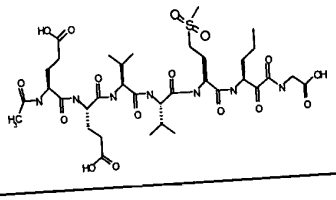
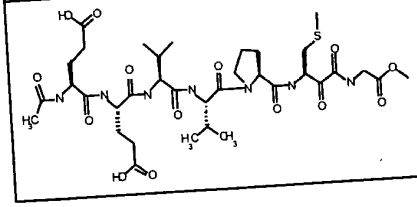
(43) Please replace page 140 with:

	Ac-EEVVP-nV-(CO)-G-propynylamide ~~(SEQ ID NO: 58)~~	c
	Ac-EEVVP-nV-(CO)-G-Am ~~(SEQ ID NO:130)~~	c
	Ac-EEVVP-nV-(CO)-G-Propylamide ~~(SEQ ID NO: 57)~~	c
	Ac-EEVVP-G(propynyl)-(CO)-G-Oallyl ~~(SEQ ID NO: 68)~~	b
	Ac-EEV-G(Ph)-P-nV-(CO)-G-OH ~~(SEQ ID NO:131)~~	b
	Ac-EEVV-Sar-nV-(CO)-G-OH ~~(SEQ ID NO: 10)~~	b

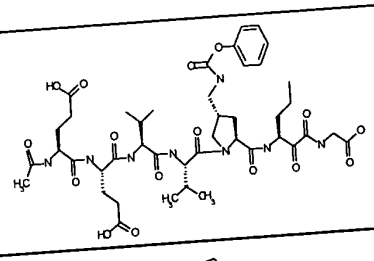
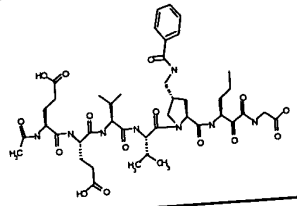
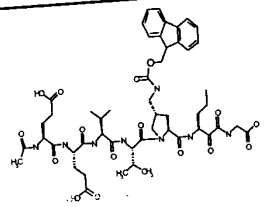
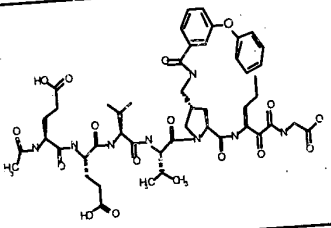
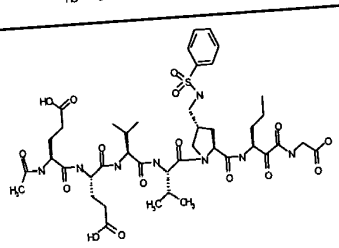
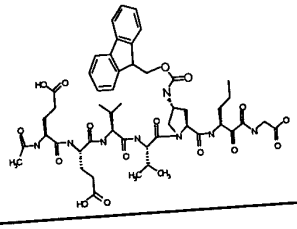
(44) Please replace page 141 with:

	Ac-EEVV-Aze-nV-(CO)-G-OH ~~(SEQ ID NO: 11)~~	a
	Ac-EEVV-P(4t-O-2AcOH)-nV-(CO)-G-OH ~~(SEQ ID NO: 132)~~	a
	Ac-EEV-G(Chx)-P-nV-(CO)-G-OH ~~(SEQ ID NO: 12)~~	a
	Ac-EEVFP-nV-(CO)-G-OH ~~(SEQ ID NO: 13)~~	b
	Ac-EEVIP-nV-(CO)-G-OH ~~(SEQ ID NO: 14)~~	a
	Ac-EEVV-dIPip-nV-(CO)-G-OH ~~(SEQ ID NO: 15)~~	a
	Ac-EEVV-Tiq-nV-(CO)-G-OH ~~(SEQ ID NO: 16)~~	a

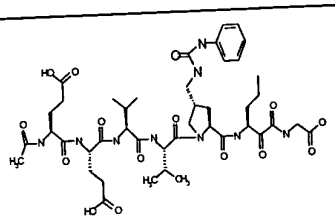
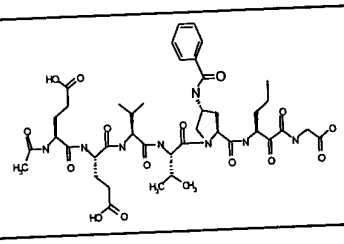
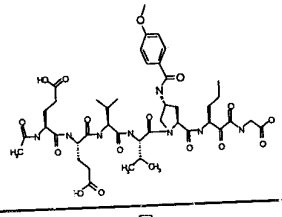
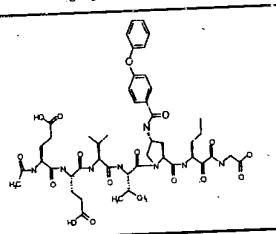
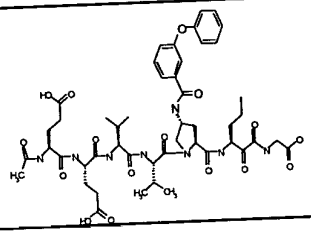
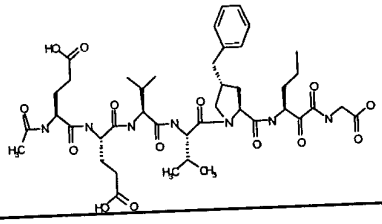
(45) Please replace page 142 with:

	Ac-EEVV-thioP-nV-(CO)-G-OH ~~(SEQ ID NO: 133)~~	a
	Ac-EEVV-C(Me)-nV-(CO)-G-OH ~~(SEQ ID NO: 17)~~	a
	Ac-EEVV-C(O2,Me)-nV-(CO)-G-OH ~~(SEQ ID NO: 18)~~	a
	Ac-EEVV-C(2-AcOH)-nV-(CO)-G-OH (SEQ ID NO: 19)	a
	Ac-EEVV-M(O2)-nV-(CO)-G-OH ~~(SEQ ID NO: 20)~~	b
	Ac-EEVVP-C(Me)-(CO)-G-OMe ~~(SEQ ID NO: 74)~~	c

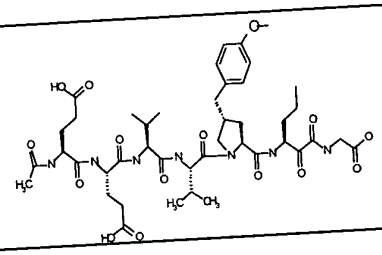
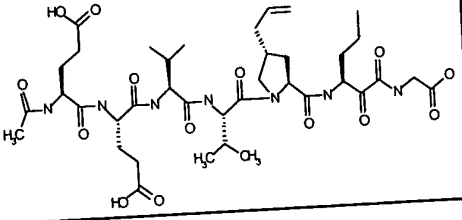
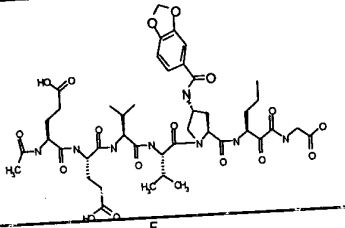
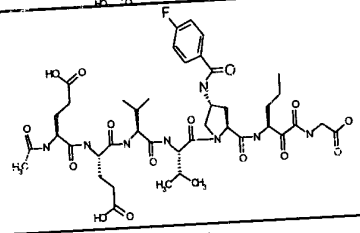
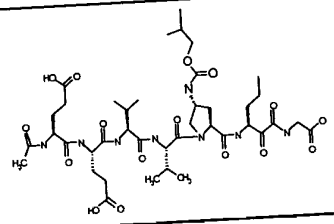
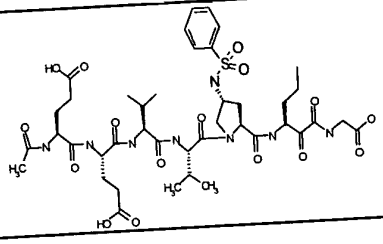
(46) Please replace page 143 with:

	Ac-EEVV-P(4t-MeNHCO2Ph)-nV-(CO)-G-OH ~~(SEQ ID NO: 97)~~	a
	Ac-EEVV-P(4t-MeNHCOPh)-nV-(CO)-G-OH ~~(SEQ ID NO: 98)~~	a
	Ac-EEVV-P(4t-MeNH-Fmoc)-nV-(CO)-G-OH ~~(SEQ ID NO: 99)~~	a
	Ac-EEVV-P(4t-MeNHBzl(3-OPh))-nV-(CO)-G-OH ~~(SEQ ID NO: 92)~~	a
	Ac-EEVV-P(4t-MeNHSO2Ph)-nV-(CO)-G-OH ~~(SEQ ID NO: 100)~~	a
	Ac-EEVV-P(4t-NH-Fmoc)-nV-(CO)-G-OH ~~(SEQ ID NO: 102)~~	a

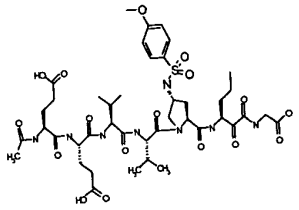
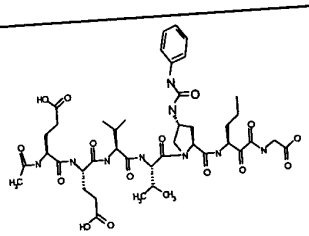
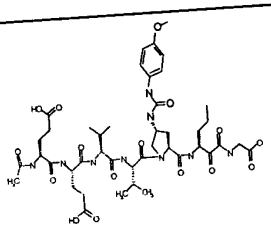
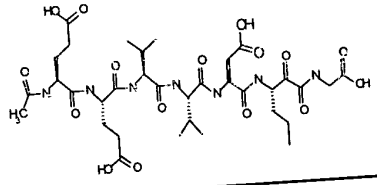
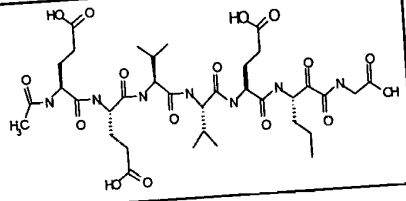
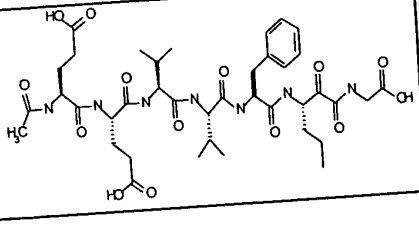
(47) Please replace page 144 with:

	Ac-EEVV-P(4t-MeUreaPh)-nV-(CO)-G-OH ~~(SEQ ID NO: 101)~~	a
	Ac-EEVV-P(4t-NHBzl)-nV-(CO)-G-OH ~~(SEQ ID NO: 103)~~	a
	Ac-EEVV-P(4t-NHBzl(4-OMe))-nV-(CO)-G-OH ~~(SEQ ID NO: 109)~~	a
	Ac-EEVV-P(4t-NHBzl(4-OPh))-nV-(CO)-G-OH ~~(SEQ ID NO: 110)~~	a
	Ac-EEVV-P(4t-NHBzl(3-OPh))-nV-(CO)-G-OH ~~(SEQ ID NO: 111)~~	a
	Ac-EEVV-P(4t-Bn)-nV-(CO)-G-OH ~~(SEQ ID NO: 21)~~	a

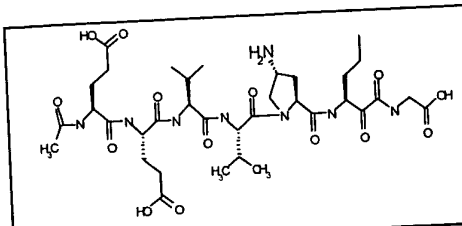
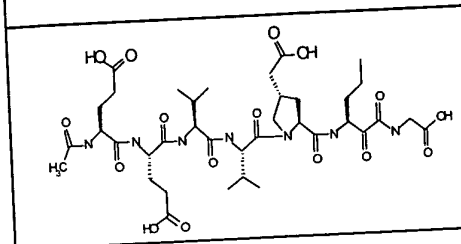
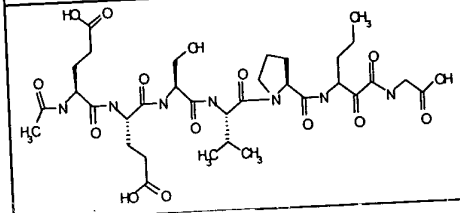
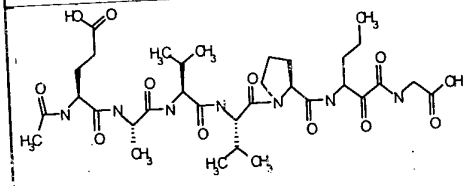
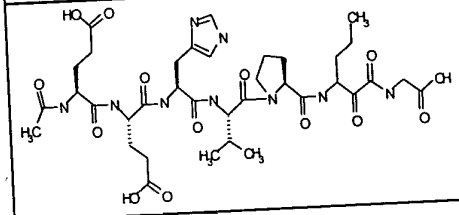
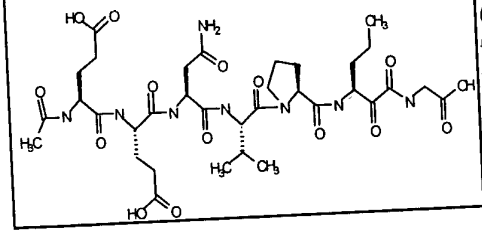
(48) Please replace page 145 with:

	Ac-EEVV-P(4t-Bn(4-OMe))-nV-(CO)-G-OH ~~(SEQ ID NO: 22)~~	a
	Ac-EEVV-P(4t-allyl)-nV-(CO)-G-OH ~~(SEQ ID NO: 23)~~	a
	Ac-EEVV-P(4t-NHBzl(3,4-OMeO))-nV-(CO)-G-OH ~~(SEQ ID NO: 112)~~	a
	Ac-EEVV-P(4t-NHBzl(4F))-nV-(CO)-G-OH ~~(SEQ ID NO: 113)~~	a
	Ac-EEVV-P(4t-NHiBoc)-nV-(CO)-G-OH ~~(SEQ ID NO: 114)~~	a
	Ac-EEVV-P(4t-NHSO2Ph)-nV-(CO)-G-OH ~~(SEQ ID NO: 115)~~	a

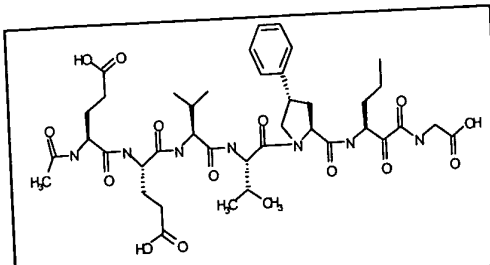
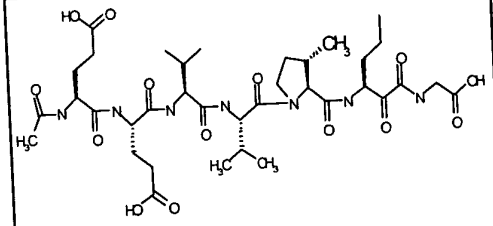
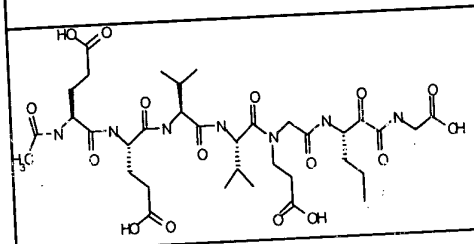
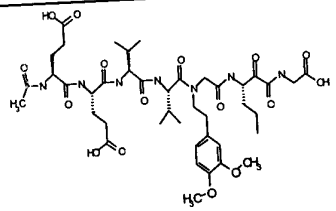
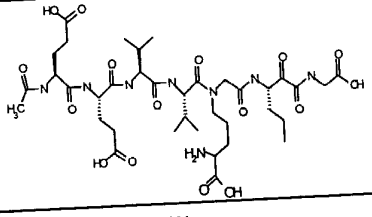
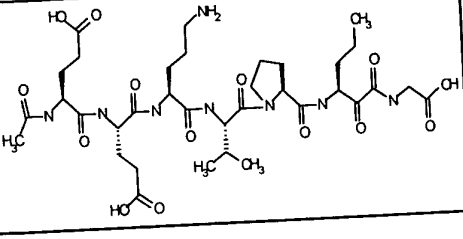
(49) Please replace page 146 with:

	Ac-EEVV-P(4t-NHSO2Ph(4-OMe))-nV-(CO)-G-OH ~~(SEQ ID NO: 116)~~	a
	Ac-EEVV-P(4t-UreaPh)-nV-(CO)-G-OH ~~(SEQ ID NO: 117)~~	a
	Ac-EEVV-P(4t-UreaPh(4-OMe))-nV-(CO)-G-OH ~~(SEQ ID NO: 118)~~	a
	Ac-EEVVD-nV-(CO)-G-OH ~~(SEQ ID NO: 24)~~	b
	Ac-EEVVE-nV-(CO)-G-OH ~~(SEQ ID NO: 25)~~	a
	Ac-EEVVF-nV-(CO)-G-OH ~~(SEQ ID NO: 26)~~	a

(50) Please replace page 147 with:

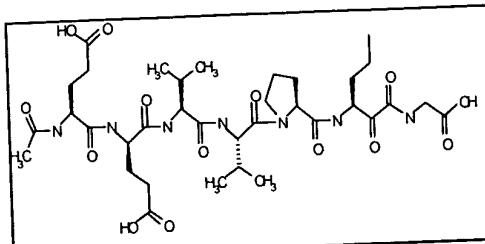
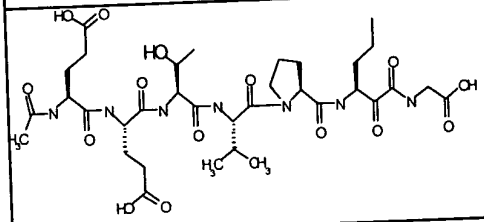
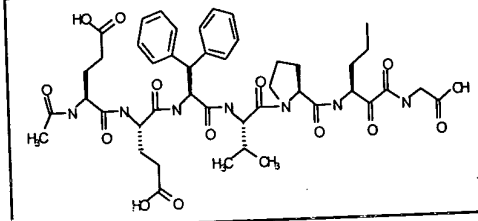
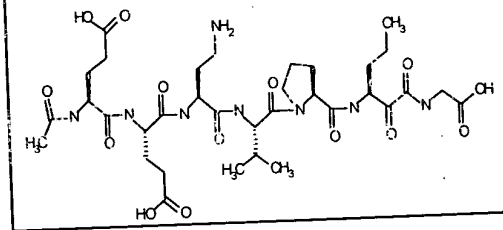
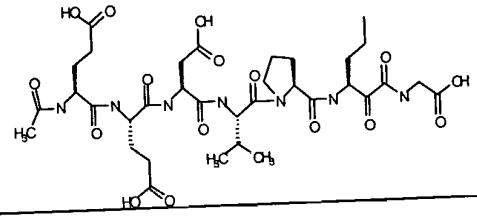
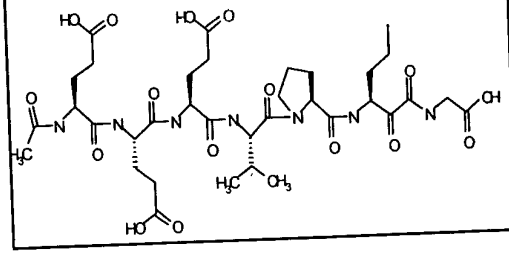
	Ac-EEVV-P(4t-NH2)-nV-(CO)-G-OH ~~(SEQ ID NO: 134)~~	b
	Ac-EEVV-P(4t-AcOH)-nV-(CO)-G-OH ~~(SEQ ID NO: 27)~~	a
	Ac-EESVP-nV-(CO)-G-OH ~~(SEQ ID NO: 28)~~	b
	Ac-EAVVP-nV-(CO)-G-OH ~~(SEQ ID NO: 29)~~	a
	Ac-EEHVP-nV-(CO)-G-OH ~~(SEQ ID NO: 30)~~	b
	Ac-EENVP-nV-(CO)-G-OH ~~(SEQ ID NO: 31)~~	b

(51) Please replace page 148 with:

	Ac-EEVV-P(4t-Ph)-nV-(CO)-G-OH ~~(SEQ ID NO: 32)~~	a
	Ac-EEVV-P(3t-Me)-nV-(CO)-G-OH ~~(SEQ ID NO: 33)~~	a
	Ac-EEVV-G(N-Et(CO2H))-nV-(CO)-G-OH ~~(SEQ ID NO: 78)~~	a
	Ac-EEVV-G(N-EtPh(3,4diOMe))-nV-(CO)-G-OH ~~(SEQ ID NO: 79)~~	b
	Ac-EEVV-G(N-Bu(4NH2,4-CO2H))-nV-(CO)-G-OH ~~(SEQ ID NO: 75)~~	a
	Ac-EE-Orn-VP-nV-(CO)-G-OH ~~(SEQ ID NO: 34)~~	b

(52) Please replace page 149 with:

- -149

	Ac-EdEVVP-nV-(CO)-G-OH ~~(SEQ ID NO: 35)~~	a
	Ac-EE-(s,s)alloTVP-nV-(CO)-G-OH ~~(SEQ ID NO: 36)~~	a
	Ac-EE-Dif-VP-nV-(CO)-G-OH ~~(SEQ ID NO: 37)~~	a
	Ac-EE-daba-VP-nV-(CO)-G-OH ~~(SEQ ID NO: 38)~~	b
	Ac-EEDVP-nV-(CO)-G-OH ~~(SEQ ID NO: 39)~~	c
	Ac-EEEVP-nV-(CO)-G-OH ~~(SEQ ID NO: 40)~~	b

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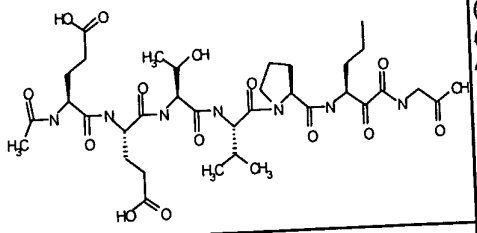
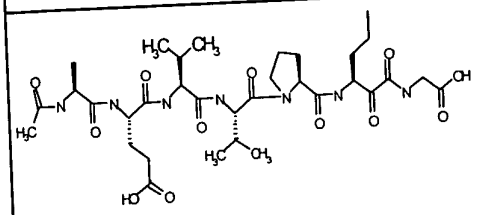
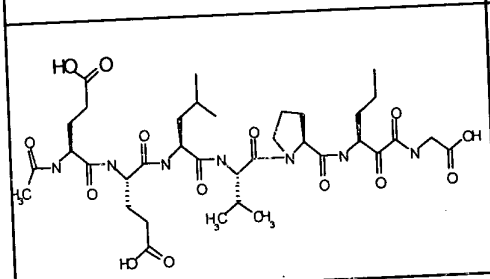
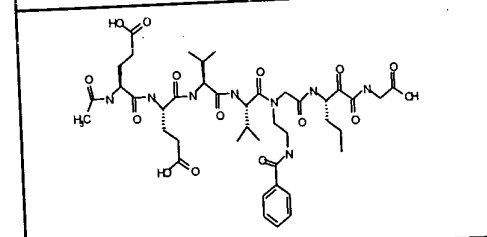
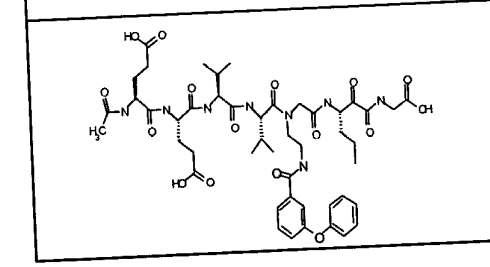
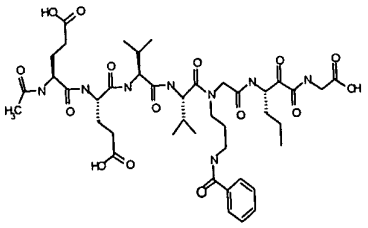
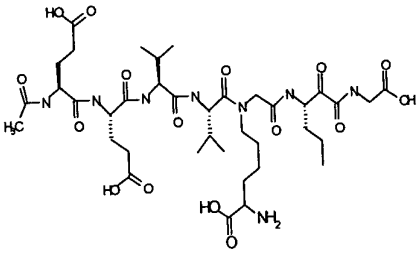
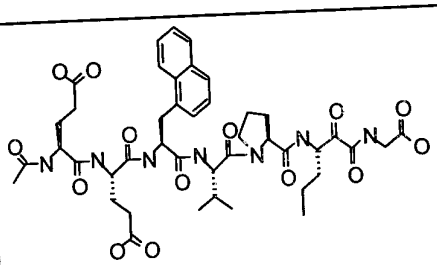
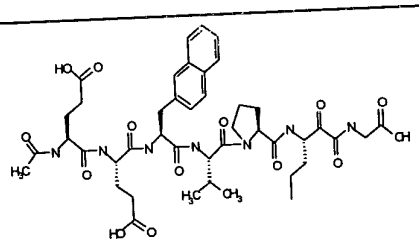
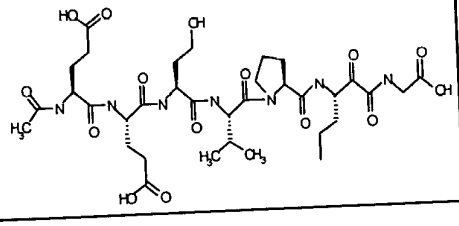
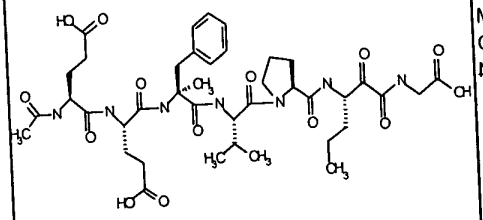
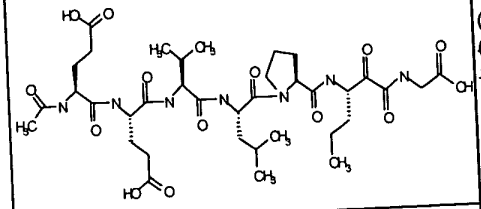
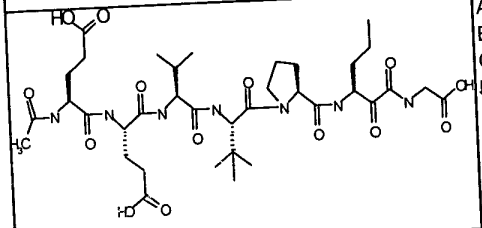
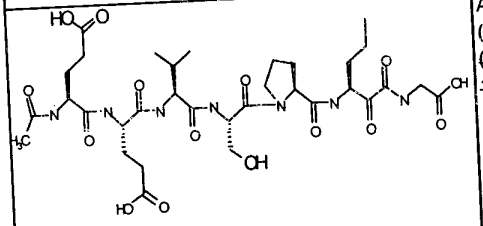
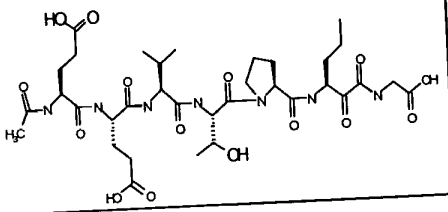
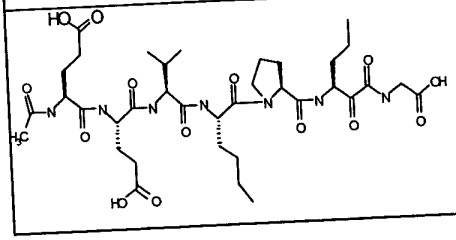
(53) Please replace page 150 with:

	Ac-EETVP-nV-(CO)-G-OH ~~(SEQ ID NO: 41)~~	b
	Ac-AEVVP-nV-(CO)-G-OH ~~(SEQ ID NO: 42)~~	b
	Ac-EELVP-nV-(CO)-G-OH ~~(SEQ ID NO: 43)~~	a
	Ac-EEVV-G(N-Et(NHBz))-nV-(CO)-G-OH ~~(SEQ ID NO: 81)~~	b
	Ac-EEVV-G(N-Et(NHBzl(3-OPh)))-nV-(CO)-G-OH ~~(SEQ ID NO: 85)~~	a

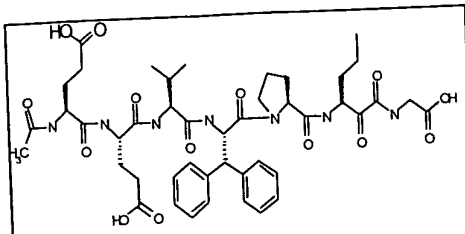
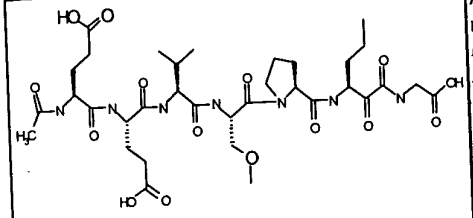
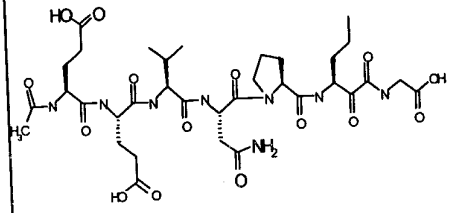
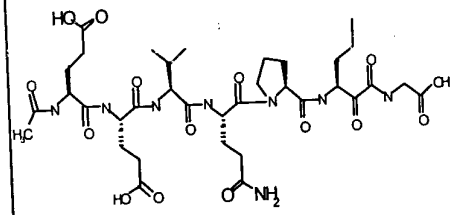
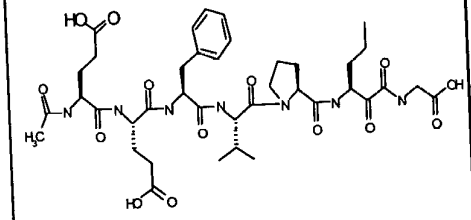
(54) Please replace page 151 with:

	Ac-EEVV-G(N-Prop(NHBz))-nV(CO)-G-OH ~~(SEQ ID NO: 86)~~	b
	Ac-EEVV-G(N-Pe(5-NH2,5-CO2H))-nV-(CO)-G-OH ~~(SEQ ID NO: 80)~~	a
	Ac-EEA(1-Np)VP-nV-(CO)-G-OH ~~(SEQ ID NO: 135)~~	b
	Ac-EEA(2-Np)VP-nV-(CO)-G-OH ~~(SEQ ID NO: 136)~~	b
	Ac-EEhSVP-nV-(CO)-G-OH ~~(SEQ ID NO: 28)~~	c

(55) Please replace page 152 with:

	Ac-EEF(alpha-Me)VP-nV-(CO)-G-OH ~~(SEQ ID NO: 137)~~	c
	Ac-EEVLP-nV-(CO)-G-OH ~~(SEQ ID NO: 138)~~	b
	Ac-EEVG(t-Bu)P-nV-(CO)-G-OH ~~(SEQ ID NO: 139)~~	a
	Ac-EEVSP-nV-(CO)-G-OH ~~(SEQ ID NO: 140)~~	c
	Ac-EEVTP-nV-(CO)-G-OH ~~(SEQ ID NO: 141)~~	c
	Ac-EEV-nL-P-nV-(CO)-G-OH ~~(SEQ ID NO: 142)~~	b

(56) Please replace page 153 with:

	Ac-EEVDifP-nV-(CO)-G-OH ~~(SEQ ID NO: 143)~~	b
	Ac-EEVS(Me)P-nV-(CO)-G-OH ~~(SEQ ID NO: 144)~~	c
	Ac-EEVNP-nV-(CO)-G-OH ~~(SEQ ID NO: 145)~~	c
	Ac-EEVQP-nV-(CO)-G-OH ~~(SEQ ID NO: 146)~~	c
	Ac-EEFVP-nV-(CO)-G-OH ~~(SEQ ID NO: 147)~~	b

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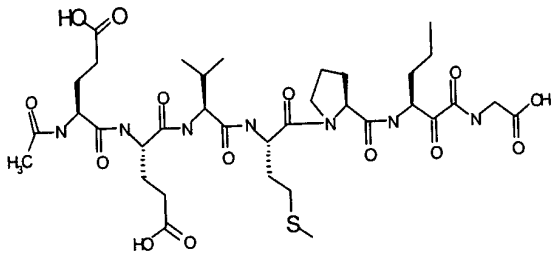
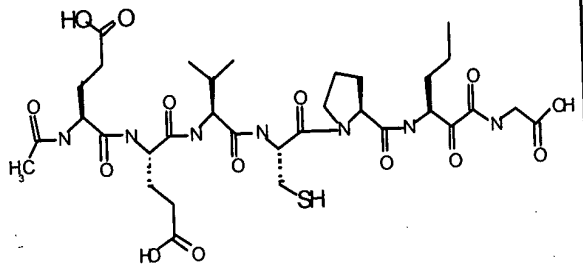
(57) Please replace page 154 with:

	Ac-EEVMP-nV-(CO)-G-OH ~~(SEQ ID NO: 148)~~	b
	Ac-EEVCP-nV-(CO)-G-OH ~~(SEQ ID NO: 149)~~	b

Respectfully submitted,

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Registration No. 34,634
Attorney for Applicant(s)

February 10, 2003
Schering-Plough Corporation
Patent Department; K-6-1, 1990
2000 Galloping Hill Road
Kenilworth, NJ 07033

I hereby certify that this correspondence is being deposited with the U.S. Postal Service First Class Mail in an envelope addressed to the Assistant Commissioner for Patents, Washington, D.C. 20231 February 10, 2003.

Palaiyur S. Kalyanaraman
Registered Representative